DR ARTURO VEGA-BEYHART (Orcid ID : 0000-0003-0373-1573)

DR JUAN M LÓPEZ-NAVARRO (Orcid ID : 0000-0001-8395-3269)

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Quality of life is significantly impaired in both secretory and non-functioning pituitary adenomas

Short-Title: Quality of life in pituitary adenomas.

Arturo Vega-Beyhart[1], Víctor Manuel Enriquez-Estrada[1], Omar Yaxmehen Bello-Chavolla[1], Tania Raisha Torres-Victoria[1], Froylan David Martinez-Sanchez[1], Juan Manuel Lopez-Navarro[1], Mireya Citlali Perez-Guzman[1], Jose Miguel Hinojosa-Amaya[1], Andrés León-Suárez[1], Hector Donaldo Espinoza-Salazar[1], Paola Roldán-Sarmiento[1], Miguel Angel Gómez-Samano[1], Francisco J. Gomez-Perez[1], Daniel Cuevas-Ramos[1]

[1]Neuroendocrinology Clinic, Department of Endocrinology and Metabolism. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán

Correspondence to:

Daniel Cuevas-Ramos. Department of Endocrinology and Metabolism. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Vasco de Quiroga 15, Sección XVI, Tlalpan 14000, México City, México. Tel. +52 (55) 56554523 Email: ceptamim@gmail.com

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SUMMARY

Objective: To evaluate the quality of life (QoL) in patients with pituitary adenomas in comparison with healthy Mexican population QoL scores.

Design & Measurements: Cross-sectional study using the short form 36 questionnaire (SF-36) in 175 patients with pituitary adenomas grouped by adenoma subtype and disease activity, and compared them with the healthy Mexican population normative QoL scores.

Patients: 44 patients with non-functioning pituitary adenomas (NFPA), 48 with acromegaly, 53 with prolactinomas and 30 with Cushing disease (CD) were enrolled in this study.

Results: Mental and physical components scores (MCS & PCS) of SF-36 questionnaire were lower in patients with active disease in all adenoma subtypes ($p<0.03$). A significant negative relationship between prolactin levels and MCS ($r= -0.30$, $p<0.01$) and PCS ($r=-0.41$, $p<0.01$) were found in prolactinomas. Patients with CD showed 24h urine free cortisol levels negatively correlated with MCS ($r=-0.43$, $p <0.01$) but not with PCS. No significant correlation was found between IGF-1ULN and

QoL scores in acromegaly. NFPA patients had lower QoL scores than patients with controlled CD, acromegaly or prolactinoma ($p < 0.02$). Active CD and prolactinoma have lower QoL scores in comparison of NFPA ($p < 0.05$). Having an adenoma, secretory or non-functional, decrease QoL scores in comparison of results in the healthy Mexican population register. Using an adjusted-multivariate model, we confirmed that disease activity in all secretory adenomas is an independent risk factor, reducing SF-36 scores significantly.

Conclusion: Activity in all secretory pituitary adenomas' patients decrease mental and physical QoL. However, independently of disease activity, secretory and NFPA significantly decrease QoL in comparison with healthy Mexican population QoL register.

Keywords: Pituitary adenomas, quality of life, short form 36 questionnaire, acromegaly, Cushing disease, prolactinoma, non-functioning pituitary adenomas.

INTRODUCTION

Quality of life (QoL) is defined as patient's health wellbeing related to physical, emotional and social aspects, implying an objective and subjective judgment about how an individual feels, functions and responds in daily life[1,2]. In the past years, QoL has been explored in patients with pituitary tumors. The purpose is to evaluate issues and interventions that are not routinely explored, providing information about the clinical impact of the disease, and leading to multidisciplinary treatments to improve the perception of the tumor pathology. There are two types of validated questionnaires to evaluate QoL in patients with pituitary adenomas. First, the generic questionnaires that can be applied to general population, and results can be compared between patients with different diseases. Examples are the

Nottingham Health Profile, the Psychological General Well Being Scale (PGWBS), and the Short Form Questionnaire 36 (SF-36)[1]. The other group of questionnaires are more disease-specific. In patients with pituitary tumors we have the Acro-QoL[3], the Cushing-QoL[4], and the Leiden Bother and Needs (LBNQ-Pituitary)[5] questionnaires. These evaluations are more sensitive to detect QoL problems related to the disease itself, but the disadvantage is that results are not comparable with other diseases or with results in general population.

Several studies have concluded that QoL is decreased when patients have a pituitary adenoma [4,6–12]. However, results are inconsistent about improvement of QoL after disease control. Some studies reported better QoL scores[1, 4, 13] whereas others reported QoL scores without change [11,12,14–16]. While some studies showed a negative correlation between serum hormone levels related with disease activity and lower QoL scores[11, 13], others found no significant correlation[3, 17]. Such inconsistent results increased the debate, and currently, it is unknown the magnitude of QoL impairment between secretory and non-functioning pituitary adenomas (NFPAs). Also, it is unclear the independent factors significantly associated with lower QoL[10,18-19], and if having a NFPA impairs QoL in comparison with otherwise healthy population without pituitary disease. Therefore, this study aimed to evaluate QoL scores of patients with secretory pituitary adenomas and compared such scores with NFPA patients. In addition, we compare all QoL scores of patients with secretory and NFPA with those in the healthy Mexican population normative.

MATERIALS AND METHODS

Patients

We conducted a comparative, cross-sectional study, with prolective evaluation in all cases. Included patients were those with confirmed pituitary adenoma diagnosed by magnetic resonance imaging, attending to the Neuroendocrinology outpatient clinic, at the Instituto Nacional de Ciencias

Médicas y Nutrición Salvador Zubirán, from August 2016 to December 2017. Flow diagram of subject progress through the study is shown in supplementary figure 1. We exclude patients without adenoma or who had non-tumoral pathology (i.e., pituitary abscess, hypophysitis, pituitary apoplexy, craniopharyngioma, or Sheehan syndrome). Elimination criteria included psychiatric disorder and inability to answer the survey (i.e., physical or intellectual disability). All subjects gave their written informed consent before inclusion to the study. The Institutional Human Biomedical Research Committee approved the study, and written informed consent was obtained from all participants. This clinical research was carried out in accordance with the principles expressed in the Declaration of Helsinki.

Biochemical criteria for disease activity

Patients with hormone hypersecretion due to pituitary adenoma were grouped according to disease activity. Patients with acromegaly were considered controlled when insulin-like growth factor-1 (IGF-1) serum levels were less than 1.2x the upper limit value (ULN) adjusted for gender and age, together with a growth hormone (GH) nadir below 0.4 mg/L during 2 h glucose tolerance test (TTOG) after 75 g load. Patients could be under cabergoline treatment, after surgery or radiotherapy (table 1). Serum GH and IGF-1 were measured with an ultrasensitive chemiluminescence immunoassay (ACCESS, Beckman Coulter®, Germany). Patients with Cushing disease were considered controlled when 24h urinary free cortisol was below the upper assay reference value of 140 μg/day, together with morning cortisol level of <1.8 mcg/mg at 8:00 h after 1 mg dexamethasone at 23:00 h in the previous night. Free cortisol was measured using a competitive union immunoenzymatic assay (ACCESS cortisol reagent pack, Beckman Coulter®, Germany). Criteria for biochemical control in patients with prolactinoma was serum prolactin (PRL) below 26 ng/mL for women, and 20 ng/mL for men. The PRL determination was performed with a chemiluminescence immunoassay (ACCESS prolactin Beckman Coulter®, Germany) with a detection limit of 0.25-20000

ng/mL. No cases with thyrotropinoma were included. Those patients with a secreting pituitary adenoma who did not meet these criteria were considered with active disease. Lastly, patients with pituitary adenoma on MRI, without a clinical syndrome or biochemical hypersecretion, were diagnosed with NFPA. NFPA patients were used as first group for statistical comparison because of lacking hormone but having symptomatology related with harboring a pituitary tumor, which may reduce QoL. After comparing NFPA patients with and without surgery and/or medical therapy (radiotherapy, and/or cabergoline), we did not identify any clinical or biochemical statistical differences between them. Therefore, all NFPA patients were used as unique group.

Evaluation of clinical variables

Baseline patient characteristic were evaluated in addition to complete physical examination (i.e., blood pressure, weight, height, visual campimetry, acanthosis nigricans, acne, hirsutism, and arthralgias). In order to adequately complete SF-36 questionnaires, some comorbidities like diabetes mellitus, arterial hypertension, obesity, lipids alterations, osteoporosis, stroke, autoimmune diseases, cardiopathy, and malignant cancer were also registered in all patients as binary variables (present/absent). Time from beginning of symptomatology, from diagnosis of pituitary adenoma, and from first medical or surgical treatment were also considered. Medical, surgical and radiation treatments for the pituitary adenoma were also documented. Imaging findings were taken from the closest magnetic resonance imaging (MRI) to the questionnaire evaluation, within the last 6 months. Tumor volume was evaluated using ellipsoid formula = 0.5 (length x width x height) = (mm^3)[21]. For cavernous sinus invasion we used Knosp classification, consisting in five grades depending on invasiveness of the adenoma. Grade 0 is when the adenoma is not invasive; grade 1 when adenoma extends less than 25%, and it does not reach the median line; grade 2

when tumor extends 50%, usually beyond the median line, but does not extend beyond lateral line; grade 3 when tumor extends about 75%, usually beyond the lateral line; and finally the grade 4 when the adenoma encase carotid artery[22]. Laboratory tests included GH, IGF-1, thyrotropin, total thyroxine, prolactin, adrenocorticotropin (ACTH), serum morning cortisol, luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol in women, and testosterone in men. Hormone levels were measured, without treatment. Hypogonadism was diagnosed based on patients' clinical symptoms, low testosterone in men, or low estrogen in women, together with inappropriate normal or low gonadotropins (table 1). Hormone replacement therapy were given in order to correct symptoms and biochemical abnormalities. Adrenal insufficiency was diagnosed clinically and biochemically as well, with low cortisol level, and low or inappropriate normal ACTH level. Steroid replacement was given after diagnosis. Hypopituitarism was defined with one or more hormone deficiencies, and panhypopituitarism in those cases with deficit of all anterior pituitary hormones. We completed biochemical evaluation with 25-OH-vitamin D, creatinine, glycated hemoglobin (A1C), and fasting insulin, since these parameters when abnormal may also decrease QoL scores.

Healthy Mexican population registry (HMPR)

We compared the QoL scores in patients with secretory and NFPA with those QoL scores reported in the Healthy Mexican Population Registry (HMPR) as reference information. These data come from the Mexican survey of access. This survey, evaluated quality of health services in two states of Mexico, which was conducted from 1999 to 2000[20]. The survey was based on a multistage randomized sampling that considered four stages and encompassed both rural and urban areas. A total of 1,200 dwellings were randomly selected in rural areas and 3,000 in urban areas. In both

urban and rural areas, an additional 10% was evaluated in order to ensure sample size. The SF-36 questionnaire was answered by 5961 normal-weight individuals, over 25 years of age, with at least one individual per household. Exclusion criteria for this group included any patient with diagnosis or treatment for chronic or acute illness disease at the moment of questionnaire evaluation. Women have 46.6 ± 13.4 years, and men 47.9 ± 13.8 years. Since the majority of our patients with pituitary adenoma were female (75%), we considered necessary to compare the baseline characteristics and QoL scores in all HMPR vs. only the group of females in the HMPR. No significant differences were found (supplementary table 1). Therefore, our HMPR reference full group is suitable for statistical comparison with our cohort of patients with pituitary adenomas even though the majority were females.

Assessment of QoL

QoL was assessed using the self-administered generic instrument SF-36 health questionnaire in the translated and validated version for Mexican population[20]. The questionnaire items are formulated as statements to evaluate eight specific health scales which are physical functioning, physical pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. Each item can be answered by choosing from 5 possible responses. A higher score value indicates a better health. Scales result calculating the average of each item's scores, so the lowest and highest scores are 0 and 100, respectively. Scales are classified in physical (PCS) and mental component scores (MCS). Using Cronbach's alpha coefficient, the SF-36 survey showed high internal consistency reliability of 0.93 to 0.78, which is greater than the minimum recommended of 0.70[23]. QoL was evaluated once the patients were with the necessary hormone replacement therapy. The questionnaire was self-answered when patients attended their medical appointment to our clinic. Average time to answer the questionnaire is 7 minutes.

STATISTICAL ANALYSES

Continuous data with normal and non-normal distribution is expressed with arithmetic means and standard deviations (SD), or medians and interquartile ranges, respectively. Categorical variables are expressed with frequencies and proportions. Linearity, normality, homoscedasticity and absence of multicollinearity were checked. Differences in sociodemographic, treatment, comorbidities, biochemical, imaging, and SF-36 scales among adenomas subtypes grouped by disease activity were assessed with student t-test, Mann-Whitney U, and chi-squared test, as appropriate. Kruskal-Wallis test was used to analyze differences in QoL across secreting adenomas subtypes, grouped by MCS and PCS. Then, we performed Spearman's correlation to assess the lineal association between hormones related with disease activity in each adenoma subtype with MCS or PCS scores. Those variables with a significant correlation were then included on stepwise multiple lineal regression models to identified independent parameters related with impaired QoL. SF-36 scores were also compared with those scores obtained from Mexican normative values of the SF-36 questionnaire[20]. We performed a single radar chart to evaluate median scores of each SF-36 scale in Mexican population survey with those QoL scores in each secretory and non-functional pituitary adenoma (figure 4). A two-tailed level of $p<0.05$ was considered significant. We used the Statistical Package for Social Sciences software (SPSS, version 24.0, Chicago, IL).

RESULTS

Baseline characteristics

We evaluated 175 patients with secretory and non-functional pituitary adenomas (table 1). They were grouped according to disease activity. Mean age was 44±14 years. Pituitary adenoma was diagnosed at 36±14 years, with a median disease duration of 7 (1-10) years. No significant difference was found in age between subtypes of pituitary adenomas (table 1). The majority of our

patients were females (n=132, 75%). More than half of patients (n= 130, 74%) had overweight or obesity. Disease was under control in 117 patients (67%) at study evaluation, and 125 patients (71%) were already with replacement therapy related with their pituitary dysfunction. In addition to neurosurgery (n=76, 1 surgery, n= 63; 2 surgeries, n=9; 3 surgeries n=4), and stereotactic radiotherapy (n=37), available medical therapy for patients with pituitary adenoma or its related hypersecretion were cabergoline, and ketoconazole. Patients with NFPA that received radiotherapy, had residual tumor after surgery. This, and other baseline characteristics are summarized in table 1.

Quality of life in secreting pituitary adenomas

Patients with biochemical uncontrolled laboratories because of pituitary hormone hypersecretion and disease activity showed significant lower mental (MCS) and physical components scores (PCS) in the SF-36 survey, than those cases with controlled disease (all $p<0.03$). These was consistent for all subtypes of pituitary adenomas. Active Cushing disease (CD) showed lower MCS in comparison of active prolactinomas (figure 2, $p<0.01$). Active CD and acromegaly showed significant lower PCS in comparison of active prolactinomas or NFPAs (figure 2, $p<0.03$). NFPAs therefore have higher PCS vs. active CD or acromegaly ($p <0.01$, figure 2). Interestingly, patients with controlled prolactinomas and controlled CD, showed higher scores in 6 out of 8, and 7 out of 8 scales, respectively ($p<0.03$, figure 1). This was not the case in acromegaly since it persisted with low scores in 5 out of 8 scales, despite active or controlled disease. The three scales that showed higher scores in controlled acromegaly patients were in the limitations due to physical (RLP) and emotional (RLE) problems, in addition to the emotional well-being scale (EWB, figure 1). All secretory adenoma but acromegaly showed higher QoL scores after disease control, however, NFPAs persisted with significant lower MCS (figure 2, $p< 0.03$), and less PCS in comparison of CD and prolactinomas. Supplementary table 1 summarized the mean of PCS and MCS for each subtype of pituitary adenoma grouped by disease activity.

Correlation between biochemical serum parameters and QoL scores

Prolactin levels showed a significant negative correlation with QoL in both MSC (r=-0.31, p= 0.01) and PCS (r=-0.41, p=0.002, figure 3) in patients with prolactinomas. Similarly, in patients with CD, urinary 24h free cortisol correlated inversely with MCS (r=-0.43, p=0.01), and we saw a statistical trend with PCS (r= -0.32, p=0.08). No significant correlation was found between IGF-1 levels (adjusted for age and gender) and MCS (r=-0.23, p=0.11) or PCS (r=-0.21, p=0.14) in acromegaly (figure 3).

Independent parameters determining impaired QoL

We performed a stepwise linear regression analyses grouped by subtype of pituitary adenoma to identified significant independent parameters that may explained the reduced QoL (table 2, supplementary figure 2). PCS was lower in acromegaly with previous pituitary surgery (β=-13.5, p= 0.01), and diagnosis of hypogonadism (β=-17.6, p<0.01). MCS was lower with active acromegaly (β=-13.7, p=0.03). Male gender (β=21, p<0.01), and control of acromegaly activity (β=19.8, p=0.04), significantly determined higher MCS and PCS, respectively. In active CD, the 60% of the impaired MCS was explained because of lower HDL (β=-0.98, p<0.01), pituitary surgery (β=-30.3, p=0.04), and visual defects in campimetry (2 out of 7 patients, 28%, β=-45.6, p<0.01, R^2 = 0.60, p<0.001). The linear multivariate regression analyses showed that active CD (β=-22, p=0.04), high HbA1c (β=-18.5, p=0.01), and lower HDL level (β= -0.77, p= 0.03) determined lower PCS. In prolactinomas, PCS and MCS were lower because disease activity (β=-16.7, p= 0.002) and visual defects (β=-21, p= 0.009). Central adrenal insufficiency also caused decreased PCS (β=-12.5 p= 0.01). Having a micro vs. macroadenoma showed better MCS (β=21, p<0.01). Independent parameters related with lower PCS in patients with NFPAs were younger age (β=-0.38, p=0.03), BMI (β=-

1.37, p=0.04), and previous diagnosis of malignant cancer (β=-27, p=0.03). No significant associations were identified to predict lower MCS. Radiotherapy was not associated with lower QoL in any pituitary adenoma.

QoL between pituitary adenomas vs. Healthy Mexican Population Registry (HMPR)

SF-36 results of our cases with pituitary adenomas were compared with those SF-36 results in the HMPR (figure 4). These otherwise healthy subjects responded the SF-36 quite similar throughout the 8 scales and their components. In summary, harboring a secretory or non-functional pituitary adenoma decrease both PCS and MCS (supplementary table 1, and figure 2) even after biochemical control. Interestingly, patients with NFPA had more QoL impairment than cases with controlled prolactinoma. This information is summarized in supplementary table 1.

DISCUSSION

We evaluated QoL in a cohort of 175 patients with secretory and non-functioning pituitary adenomas grouped by disease activity. Then, we compare our results with those registered in the HMPR[20]. We confirmed that all subtypes with active pituitary adenomas have reduced QoL. However, despite normalization of hormone hypersecretion, QoL remain lower than Mexican general population. In fact, NFPAs also showed lower QoL than healthy people. Therefore, harboring a pituitary adenoma, secretory or not-secretory, significantly impaired the QoL of a given individual. The independent and significant parameters related with reduction of QoL were also explored, and we found specific and novel parameters for each type of pituitary adenoma.

Decrease of physical component score (PCS)

PCS was particularly low in patients with acromegaly. Because of the acral overgrowth, musculoskeletal pain, arthritis[10], fatigue, and soft tissue swelling[18], it is feasible to explain these consistent results in our and other publications. However, no significant negative correlation was found between higher serum IGF1 levels and lower PCS. Such clinical complications are consequence of active acromegaly but usually do not improve after biochemical control having irreversible effects and therefore, patients remained with poor PCS. CD, however, usually improves after successful treatment, and symptomatology improves together with normalization of serum or urinary cortisol levels. As a result, significant negative correlation was identified between 24h urinary free cortisol with PCS. Similar benefit was seen in patients with prolactinoma, since reduction of symptomatology as consequence of medical treatment and prolactin normalization was significantly associated with improvement of PCS.

Decrease in mental component score (MCS)

MCS was especially low in patients with CD and prolactinoma. Although sometimes cortisol or prolactin levels do not correlate with disease severity, previous studies have implicated both prolactin and cortisol on human behavior with multiple psychosomatic implications[13,26]. For example, reduction on hippocampus volume, with progressive cognitive decline, increased risk of developing psychiatric illnesses such as depressive symptoms, anxiety-related disorders, and borderline personality disorder[19, 27, 28]. Also, higher cortisol levels have been significant related with poor self-esteem, low internal locus of control[29,30], loneliness and sleep deprivation[31]; while reduction in serum cortisol has been related to positive affect demonstrated after aggregating momentary experiences throughout a working or leisure day[32]. Additionally, PRL hypersecretion increased anxiety in

one study[24] by producing an imbalance of related neurotransmitters like serotonin, GABA, and dopamine[24], which also influences mood, and attitude. Clinical studies in humans have also indicated a significant correlation between higher PRL levels and psychological distress[25]. Female patients with hyperprolactinemia usually report more symptoms of anxiety and hostility than control female subjects, and additionally, patients with prolactinomas have more perception of pain, affecting their social functioning and emotional status. These variables significantly correlated with prolactin circulating levels[13].

Taking these findings together it could may explain why higher serum cortisol and prolactin significantly correlated with poor QoL results in our patients, particularly in components like social relations, mental health, and emotional role limitations. Despite significant negative correlation (figure 3), we believe PRL was not too high because our cases were uncontrolled under insufficient treatment with cabergoline. Regression model showed that having a microprolactinoma was significant and independent parameter related with higher QoL in MCS (table 2). Therefore, it is possible that in addition of the negative significant correlation of PRL with QoL (figure 3), tumor size also impacted QoL in prolactinomas (table 2).

NFPA also caused significant reduction in MCS. Although NFPA may cause hyperprolactinemia because mass effect and compression of infundibulum, prolactin usually have a more slightly to moderate elevation making necessary to find additional explanation to this outcome. Also, NFPA-related hypopituitarism may cause less QoL but usually this is when it remains symptomatic because of lack or incomplete treatment. In our clinic, a complete evaluation, treatment, and follow-up of hypopituitarism is given to all of our patients, and therefore, it is less likely that NFPA-related hypopituitarism caused poor MCS. In contrast, patients with NFPA has been associated with reduced QoL too in other studies.

Van der Klaauw et al reported worse physical ability and body pain in patients with pituitary adenomas after treatment, including NFPA[9]. However, we evaluated NFPA patients after treatment but also under clinical observation because a stable tumor without growing. In both clinical scenarios, harboring a NFPA significantly reduced MCS, therefore, further risks factors may be identified. In addition to chronic headaches, for example, scales related with MCS may be impaired because of patients are now aware that have a “head tumor”, which will may need long-term follow-up, that perhaps starts growing and require surgical treatment or radiotherapy, it may compress optic chiasm, invade carotid artery, or sometimes is complicated with an emergency called apoplexy. All this information might cause anxiety to patients with NFPA, decreasing well-being and energy, low self-stem, or depression. This scenario could also explain why all secretory pituitary adenomas remained with low QoL even with good disease control. In addition, having hormone deficits associated with NFPA may also contribute to low QoL. Usually, all anterior pituitary hormones should be evaluated to treat any deficiency, however, sometimes it is expensive, like GH-replacement therapy, or affects energy, fertility, sexuality, or increase risk for metabolic diseases, which also have been reported to decrease QoL. Recently, Andela et al. proposed that impaired quality of life in patients with NFPA results from a multi-scale situation that can be explained by the Wilson-Cleary biopsychosocial model, which states that health and QoL can be considered as a continuum of increasing biological, psychological and social complexity, with pure biological measures and general health perceptions[35]. Therefore, NFPA is a tumor that should not be considered with similar QoL as general healthy population[10, 18, 36], and clinical research using such patients as "control group" may yield misleading results.

In summary, patients with pituitary adenoma and disease activity or disease control, significantly have worse QoL outcomes [4, 13, 33].

Independent parameters significantly associated with lower QoL

Identifying independent factors related with lower QoL in patients with pituitary adenomas have been motive of constant research [1, 3, 8, 11, 37, 38]. All this information help to understand why the pituitary adenoma patients have low QoL. In our patients, we found novel risk factors that showed positive or negative impact on QoL depending on adenoma subtype and disease activity. Firstly, in acromegaly, males were less aggravated in MCS, independently of disease activity. Although the positive impact of male gender has been previously described in acromegaly and CD[1, 9, 39], this was not evaluated with or without disease activity. We found here that male gender is and independent factor related with better MCS even in patients with active acromegaly. Secondly, hypopituitarism has been significantly and independently associated with lower QoL in patients with pituitary adenoma[9, 38, 39]. Consistently, gonadotropin and ACTH deficiencies impacted negatively in global QoL scores mainly in acromegaly and prolactinomas. This result was despite good replacement therapy with estrogen in women, testosterone in male, or steroids for central adrenal insufficiency. In addition to the symptomatology of acromegaly, and hyperprolactinemia, it should be considered less QoL in such patients when hypogonadism or central adrenal insufficiency is diagnosed. The two main risk factors that decrease QoL scores in NFPA were age at diagnosis, and BMI, decreasing PCS. Also, these should be remembered as additional significant clinical features to impairs QoL. Previous pituitary surgery and visual defects were also independent and significant risk factors to reduced QoL. In our study, we do not find stereotactic radiotherapy with LINAC as a significant variable to decrease QoL. This is

emphasized because previous reports have found the conventional radiotherapy as an important negative factor related with lower QoL outcomes in acromegaly[8]. However, it is important to consider that it was only used in few patients (n=37).

SF-36 Mexican normative comparison

QoL is chronically affected in patients with pituitary adenoma even after disease control and remained lower when compared with general healthy population[9, 10,18]. However, other studies reported similar QoL in healthy people and patients with NFPA[6,15]. All of the secretory or non-functioning pituitary adenomas showed lower QoL than healthy Mexican population, and this was seen with active or disease control. Moreover, patients with NFPA also shown lower QoL than general healthy population. These results highlight that patients with pituitary adenomas, secretory or with NFPA, do not have same QoL to healthy general population and this QoL could even be more reduced when patient has active disease.

Our study has some limitations that should be stated. First, the cross-sectional design only allowed us to reached significant associations but not specific cause-effect conclusions. However, these results contribute importantly to the specific attention that patients with pituitary adenomas should receive in mental and physical components. Another limitation is that we only used a general QoL questionnaire like the SF-36 which lacks specific questions that may have a greater sensitivity in the symptomatology of patients. Nevertheless, we do not used specific QoL questionnaires for acromegaly or Cushing disease (i.e. AcroQoL or CushingQoL) in order to compare QoL between different pituitary adenomas. Finally, we evaluate a relatively small sample of patients, however, considering that some of these pituitary adenomas are quite rare we showed here sufficient number of cases to reach statistical power to do comparisons among them.

We can conclude that QoL is reduced in active pituitary disease, that persisted low in patients after controlled pituitary hormone hypersecretion, and that NFPA showed significant impairment in QoL too, despite been a non-functional tumor. It is also important to note that although patients got higher and therefore better QoL score when they reached disease control, they do not reach a QoL similar to the one scored in healthy Mexican normative system. Identifying and treating the associated independent factors is also important in order to reduce or correct the mental and physical impairments as good as possible.

AUTHOR CONTRIBUTIONS

Research idea and study design: AVB, VMEE, DCR.

Data acquisition: AVB, VMEE, TRTV, FDMS, MCPG, JMHA, HDES, ALS.

Statistical analysis: AVB, DCR, OYBC, VMEE.

Data analysis/interpretation: AVB, DCR, MAGS, FGP.

Manuscript drafting: AVB, DCR, VMEE, OYBC, DCR, MGAS, FGP.

Supervision and mentorship: DCR.

Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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FIGURE LEGENDS

Figure 1. SF-36 scales and global scores of patients with secretory adenomas grouped by disease activity. *Mann-Whitney U test $p<0.05$. PF = Physical functioning; RLP = Role limitations due to physical health; P = Pain; GH = General health; RLE = Role limitations due to emotional problems; E = Energy; EWB = Emotional well-being; SF = Social functioning; PCS = Physical component score; MCS = Mental component score.

Figure 2. SF-36 global MCS and PCS comparison among all adenoma's subtypes. Secretory adenomas comparisons are made between active and controlled disease, respectively. NFPA scores are compared with both groups. *Mann-Whitney U test $p<0.05$. MCS = mental component score; PCS = physical component score; NFPA = non-functioning pituitary adenoma.

Figure 3. Spearman correlation between biochemical parameters and SF-36 scores grouped by mental (MCS), and physical component score (PCS).

Figure 4. Single radar chart to evaluate mean scores of each SF-36 scale in HMPR with those QoL scores in each secretory and non-functional pituitary adenoma (age- and sex-paired). *Student-t test $p=0.001$ for Mexican scores vs scores in others secretory adenomas. **Student-t test $p=0.001$ for Mexican scores vs scores in others secretory adenomas except prolactinomas. *** Student-t test $p=0.001$ for Mexican score vs NFPA QoL scores.

Supplementary figure 1. Flow diagram of subject progress through the study.

Supplementary figure 2. Significant independent factors determining worse QoL outcomes using linear regression analyses. *Factors associated with both mental and physical components. **Factors associated with physical components. ***Factors associated with mental components.

Table 1. Baseline characteristics of patients studied grouped by subtype of adenoma and disease activity.

	NFPA	**Cushing disease**		**Acromegaly**		**Prolactinoma**	
n = 175	44	23	7	25	23	25	28
	-	Controlled	Active	Controlled	Active	Controlled	Active
Age at diagnosis (years)	44 (36-54)	29 (25-37)	27 (19-38)	36 (27-51)	37 (34-48)	30 (25-39)	27 (21-34)
Female	35 (79.5)	22 (95.7)	7 (100)	11 (44)	10 (43.5)	21 (84)	26 (92.9)
BMI (kg/m2)	28.3 ± 4.	29.3 ± 5.0	32 ± 3.8	31 ± 5.3	29.7 ± 5.3	27 ± 4.1	28.1 + 8.4
Panhypopituitarism [a]	8 (18.2)	3 (13)	1 (14.3)	5 (20)	2 (8.7)	1 (4)	5 (20.3)
GH deficiency	7 (15.9)	1 (4.3)	1 (14.3)	1 (4)	0 (0)	1(4)	4 (14.3)
Central hypocortisolism	11 (25.0)	10 (43.5) *	0 (0) *	8 (32)	5 (21.7)	3 (12) *	13 (46.4) *
Central hypothyroidism	6 (13.6)	1 (4.3)	2 (28.6)	3 (12)	1 (4.3)	1 (4)	5 (20.3)
Central hypogonadism	7 (15.9)	4 (17.4)	2 (28.6)	5 (20)	3 (13)	2 (8)	8 (28.6)
Macroadenoma	13 (29.5)	0 (0)	1 (14.3)	2 (8) *	13 (56.5) *	3 (12)	5 (17.9)
Invasion (MRI)	5 (11.4)	0 (0)	0 (0)	2 (8)	6 (26.1)	4 (16)	4 (14.3)
Visual defects	15 (34.1)	0 (0) *	2 (28.6) *	2 (8)	5 (21.7)	1 (4)	6 (21.4)
Neurosurgery (1-3)[b]	12 (27.2)	21 (91.2)	7 (100)	19 (76) *	11 (47.8)*	2 (8)	4 (14.3)
Cabergoline	19 (43.2)	6 (26.1)	3 (42.9)	10 (40)	15 (65.2)	22 (88)	27 (96.4)
LINAC radiotherapy[c]	5 (11.4)	7 (30.4)	3 (42.9)	15 (60) *	5 (21.7) *	1 (4)	1 (3.6)
Tumor volume (mm3)	86 (23-320)	30 (9-74)	36 (4-125)	24 (3-61)**	125 (26-400)**	22 (4-98)	27 (12-142)

NPFA: Non-functioning pituitary adenoma. Invasion: Knosp >1. Macroadenoma: >1 cm. MRI = magnetic resonance imaging. Tumor volume= 0.5 (length x width x height) = mm^3. Neurosurgery (1 surgery, n= 63; 2 surgeries, n=9; 3 surgeries n=4). ACTH: adrenocorticotropin. IGF-1: Insulin-like growth factor 1. GH: Growth hormone. *Pearson's chi-squared test (p<0.05) **Mann-Whitney U test (p<0.05), ***Student-t test (p<0.05). [a]Panhypopituitarism was defined with all hormone deficiencies. [b]76 patients underwent pituitary neurosurgery, 1 surgery = 63; 2 surgeries=9; and 3 surgeries=4. [c]Patients with NFPA that received radiotherapy had residual tumor after surgery

Table 2. Stepwise multiple linear regression analyses to evaluate independent parameters related with lower physical (PCS) and mental component scores (MCS) in each adenoma subtype

Acromegaly							
PCS				**MCS**			
Related Factor	**Beta**	**95% CI**	**p**	**Related Factor**	**Beta**	**95% CI**	**p**
Active disease	-17.646	-30.7 - -4.5	0.009	Active disease	-13.708	-26.59 - -.82	0.038
Pituitary surgery	-13.575	-24.7 - -2.4	0.018	Male	21.152	7.86 - 34.44	.003
Hypogonadism	-8.647	-2.2 - -19.1	.046	Hypogonadism	-5.985	-22.69 - 10.72	.474
Hypertriglyceridemia	10.196	-1.1 - 21.5	.116	-	-	-	-
F= 5.4, p = 0.001, R^2 =.39 y= 39 + (-13.6)X_1 + (-17.6)X_2 + (-8.6)X_3				F= 6.7, p = 0.001, R^2 =.32 y= 68 + (-13.7)X_1 + (21.2)X_2			
Cushing disease							
PCS				**MCS**			
Related Factor	**Beta**	**95% CI**	**p**	**Related Factor**	**Beta**	**95% CI**	**p**
Active disease	-21.815	-42.9 - -.72	0.043	Active disease	-20.791	-39.75 - -1.82	0.033
A1c	-18.490	-33.6 - -3.2	0.019	HDL	-.987	-1.61 - -.359	.003
HDL	-.773	-1.4 - -0.56	0.036	Pituitary surgery	-30.307	-60.09 - -.51	.046
Visual defects	-24.67	-70.6- 21.3	.280	Visual defects	-45.671	-75.38- -15.95	.004
F= 7.3, p =0.001, R^2=.46 y= 212.2 + (-21.8)X_1 + (-18.5)X_2 + (-0.8)X_3				F=9.5, p<0.001, R^2=.60 y= 141.6 + (-20.8)X_1 + (-0.98)X_2 + (-30.3)X_3 + (-45.7)X_4			
Prolactinoma							
PCS				**MCS**			
Related Factor	**Beta**	**95% CI**	**p**	**Related Factor**	**Beta**	**95% CI**	**p**
Active disease	-16.757	-27.2 - -6.2	0.002	Active disease	-20.722	-31.0 - -10.4	0.000
ACTH deficiency	-12.523	-21.3 - -3.3	0.010	Microadenoma	20.939	7.3 - 34.5	.003
Visual defects	-21.128	-36.7 - -5.5	0.009	Visual defects	-13.627	-28.52 - 1.2	.072
F= 9.3, p<0.001, R^2 =.34 y = 79.5+ (-16.8)X_1 + (-12.5)X_2 + (-21.1)X_3				F=10.5, p<0.001, R^2=.41 y= 71.7+ (-20.7)X_1 + (20.9)X_2			
Non-functioning pituitary adenoma							
PCS				**MCS**			

Related Factor	Beta	95% CI	p	Related Factor	Beta	95% CI	p
Active disease	-16.757	-27.2 - -6.2	0.039	None	-	-	-
BMI	-0.387	-21.3 - -3.3	0.041	-	-	-	-
History of cancer	-1.374	-36.7 - -5.5	0.032	-	-	-	-
$F= 6.191$, $p = 0.001$, $R^2 =.17$ $y= 172.4+ (-.387)X_1 + (-1.374)X_2 + (-27.7)X_3$